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Pesticide Fact Sheet Number 237: Oxadixyl (New Chemical Registration)

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

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EPA

Pesticide Fact Sheet

PB92-238492

Name of Chemical: Oxadixyl
Reason for Issuance: New Chemical Registration
Date Issued: February 27, 1992
Fact Sheet Number: 237

DESCRIPTION OF CHEMICAL

Generic Name: 2-methoxy-N-(2-oxo-1,3-oxazolidin-3-yl)-acet-2',6'-xylidide and its desmethyl (M-3) metabolite

Common Name: oxadixyl

Trade Name: Sandofan

EPA Shaughnessy Code: 126701

Chemical Abstracts Service (CAS) Number: 77732-09-3

Year of Initial Registration: 1992

Pesticide Type: Fungicide

U.S. and Foreign Producers: Sandoz Crop Protection Corporation

USE PATTERNS AND FORMULATIONS

APPLICATION SITES: Seed treatment only. Seeds of the crop groupings fruiting vegetables (except cucurbits) group, cucurbit vegetables group, leafy vegetables (except Brassica vegetables) group, Brassica (cole) leafy vegetables group, cotton seed, peas, soybeans, sunflower seed, root and tuber vegetables group, cereal grains group (except wheat), grass forage, fodder and hay group, and non-grass animal feeds (forage, fodder, straw and hay) group for the control of Pythium and suppression of Phytophthora caused seed and seedling diseases.

METHOD OF APPLICATION: Application will be made by commercial seed treaters as a water-based slurry through standard application equipment.

TYPES OF FORMULATIONS: 31% flowable end-use (EUP) formulation and 96% technical (MUP) product for formulating use.

APPLICATION RATES: Application rates range from 0.25-0.75 ounce

active ingredient/100 pounds of seed.

USUAL CARRIER: water.

SCIENCE FINDINGS

Summary Science Statement

Available acute toxicity studies indicate that oxadixyl is in toxicity category III (Caution) for acute oral, acute dermal, acute inhalation and primary eye irritation.

Chronic feeding/oncogenicity studies were conducted in both the rat and mouse. The chronic feeding study in the rat suggests that the target organ for toxicity is the liver. There was a statistically significant increase in hepatocellular adenomas at the highest dose tested in both male and female rats. In the chronic feeding study on mice, a statistically significant increase in relative liver weights in male and female mice was observed but no carcinogenic effects were seen.

Oxadixyl did not induce either genotoxic effects or chromosomal aberrations in a series of mutagenicity studies. Teratology studies indicated a NOEL of 200 mg/kg body weight in rabbits and in rats the maternal NOEL was 250 mg/kg/day and developmental NOEL was 500 mg/kg/day.

Environmental fate laboratory data have been reviewed and most were found to be acceptable. Oxadixyl is slowly degraded in soil, with a half-life of about 16 months. Oxadixyl was mobile in loamy sand, intermediate in sandy loam and loam and low in clay. Oxadixyl has a potential to leach, especially in soils high in sand content and/or low in organic matter. Field crop rotational studies and soil dissipation studies have been completed but not yet submitted for review. The data base is considered acceptable to support the seed treatment use, since that use should not result in significant levels of the chemical entering the environment.

Use of the product as a seed treatment provides no significant acute, subacute or chronic risks to non-target organisms, including endangered or threatened species.

CHEMICAL CHARACTERISTICS

PROPERTY	MUP	EUP
Color	beige	off-white
Physical state	crystalline solid	liquid
Odor	odorless	slight
Bulk density	0.5 kg/l	
Specific gravity		1.06
pH	5.6	8.0-8.5
Storage stability	28 months	>2 years

TOXICOLOGICAL CHARACTERISTICS

Acute Effects:

Acute oral toxicity in rats:
LD_{50} - 3,622 mg/kg in males
1,803 mg/kg in females
Toxicity category III
Acute dermal toxicity in rats:
LD_{50} - >2,000 mg/kg (male and female)
Toxicity category III
Acute inhalation toxicity in rats:
LC_{50} - >5.6 mg/l/6hrs
Toxicity category III
Primary eye irritation in rabbits:
Toxicity category III
Primary dermal irritation in rabbits:
Toxicity category IV
Dermal sensitization in Guinea pigs:
Not a skin sensitizer

Chronic studies:

Rodent Feeding/Oncogenicity:

1. A 2-year feeding/oncogenicity study with male and female rats using dietary concentrations of 0, 100, 250 and 1,000 ppm, equivalent to 0, 4.79, 10.9 and 47.9 mg/kg/day, was conducted. There was a statistically significant increase in hepatocellular adenomas at the high dose in both males and females. No evidence of early onset of these tumors was seen since no hepatocellular adenomas or carcinomas were seen in any animals sacrificed at 55 and 81 weeks. Historical control data indicated that the spontaneous rate for hepatocellular adenomas was 1.64% for males and 2.62% for females. Incidence of this tumor type at the highest dose tested was much greater than the historical controls for both males and females. Survival was unaffected in males and was slightly but statistically significantly better in females. Liver weights were significantly increased in males but not females at the high dose. Mean body weights were slightly increased in males but 2-10% lower in females at the high dose.

The HED Peer Review Committee considered the classification of oxadixyl according to EPA Guidelines for Carcinogen Risk Assessment and tentatively classified the chemical as a Group C oncogen since its administration was associated with a significantly increased incidence of benign tumors in male and female rats at high doses. The committee requested that the liver slides from this test be submitted for reevaluation. The basis for this request was that, although there was a very strong response for liver tumors at the high doses, all of the tumors were diagnosed as benign. The only hepatocellular carcinoma diagnosed was found in a control, male rat. The reevaluation of the liver slides indicated a shift from mostly benign to mostly malignant tumors due to a difference in classification schemes used by the pathologists. Upon reconsideration, the Committee felt that a quantification of risk was warranted in light of the mostly malignant and strong liver tumor response seen in both sexes of rats. The Committee

recommended that the quantification of risk be performed using the original combined benign and malignant liver tumor numbers since the total number of tumors would not change significantly.

The systemic NOEL in rats was 250 ppm and the systemic LEL was 1,000 ppm based on decreased body weight gain in females and increased liver weights in males. Hepatocellular adenomas were present in both male and female rats at the 1,000 ppm level.

2. A 2-year chronic feeding/oncogenicity study in mice was conducted using dietary concentrations of 0, 40, 100 and 400 ppm, equivalent to 0, 6, 15 and 60 mg/kg/day. In this study, the only effect of treatment seen was an increase in relative liver weights which was statistically significant in male and female mice at 97 weeks. There was no evidence of tumor formation at 400 ppm (highest dose tested). The systemic NOEL was 100 ppm and the systemic LEL was 400 ppm (HDT) based on relative liver weight increases in both male and female mice.

3. A 13-week feeding study in rats using doses of 0, 100, 250 and 1,000 ppm resulted in a NOEL for males of 6.6 mg/kg/day. Based on decreased hemoglobin, mean corpuscular hemoglobin, total blood protein and blood calcium, the LEL (males) was equivalent to 16.5 mg/kg/day. For females, the NOEL was 8.2 mg/kg/day. Based on decreased total blood protein, albumin, calcium and chloride, the LEL for females was 21.5 mg/kg/day.

Non-rodent Feeding Studies:

A 1-year feeding study using male and female beagle dogs was conducted at levels of 0, 25, 50 and 500 ppm (equivalent to 0, 0.625, 1.25 and 12.5 mg/kg/day). There were no definitive toxic effects in dogs fed at the highest dose tested. A significant decrease in mean thyroid weight was observed in all dosed groups of females but no effects were noted in males. This was considered an incidental finding in the absence of further supporting data. Based on the lack of systemic effects at any dose tested, the systemic NOEL was considered to be greater than or equal to 12.5 mg/kg/day.

Teratology:

1. A teratology study was conducted in rabbits by administering dosage rates of 0, 50, 100 and 200 mg/kg body weight by gavage. The maternal NOEL was 50 mg/kg and the LEL was 100 mg/kg based on increased resorptions. The teratogenic NOEL was 200 mg/kg (highest dose tested).

2. A teratology study using rats was conducted by administering levels of 0, 250, 500 or 1,000 mg/kg/day by gavage. The maternal NOEL in this test was 250 mg/kg/day and the maternal LEL (decreased body weight gain) was 500 mg/kg/day. The developmental NOEL was 500 mg/kg/day and the LEL was 1,000 mg/kg/day based on decreased fetal body weight gain, increased resorptions, increased incidence of retardation of fetal kidney development and increased incidence of skeletal variations.

Reproduction:

In a 3-generation rat reproduction study, dose levels of 0, 100, 250 and 1,000 ppm in feed resulted in a NOEL of 250 ppm (equivalent to 22 mg/kg/day for dams) for effects on reproduction and development up to lactational day 21 and an LEL of 1,000 ppm (88 mg/kg/day for dams) for weight loss on lactational day 21 in F1a and F2a pups. The NOEL for other systemic effects was 250 ppm (22 mg/kg/day) and the LEL was 1,000 ppm (88 mg/kg/day) for a marginal body weight loss and food consumption increase in females prior to mating, at conception and during lactation. Potassium and glucose levels were significantly increased in males at the highest dose tested in 2 of the 3 generations tested.

Mutagenicity:

Oxadixyl was negative for mutagenicity in the Ames Salmonella assay for point mutations, mouse micronucleus assay, Saccharomyces cerevisiae reverse mutation induction assay, Saccharomyces cerevisiae mitotic induction assay, UDS in rat hepatocytes, and transformation in Balb/C-3T3 cells.

ENVIRONMENTAL FATE

Based on available data submitted to support registration of both seed treatment and terrestrial crop use, oxadixyl is persistent and mobile in the environment. In laboratory studies, oxadixyl was stable to hydrolysis at pH 5 and 7. At pH 9, the chemical undergoes a minor hydrolytic reaction with half-lives between 7 and 52 days at 70 and 50° C respectively. The chemical is not susceptible to photolysis in water or on soil. Aerobic and anaerobic soil metabolism is apparently similar with oxadixyl being slowly degraded with a half-life of 16 months. Volatilization or degradation to CO_2 or other volatile products is not a significant dissipation pathway. Leaching studies demonstrate that the parent compound is especially mobile in soils with a high percentage of sand and/or a low organic matter content. There are no acceptable field dissipation studies that confirm these laboratory findings. The properties and characteristics that oxadixyl demonstrated in laboratory studies are similar to those associated with chemicals detected in ground water. Also, the chemical could be transported in runoff during a rain event to surface water. However, the use of oxadixyl in commercial seed treatment operations should not result in significant levels of the chemical getting into the environment. As such, the impact to surface or ground water should be minimal.

ECOLOGICAL CHARACTERISTICS

Effects on terrestrial organisms: The available data indicated that the maximum proposed seed treatment rate should not have acute effects on non-target birds and mammals. Although the maximum terrestrial EEC exceeds the reproductive and systemic NOELs for mammalian toxicity tests, potential chronic effects to birds

and mammals would be minimal due to low application rate, low toxicity, method of application (planting), low bioaccumulation potential and adequate labeling to ensure proper planting techniques.

Effects on aquatic organisms: Based on available data, it was concluded that no acute or subacute effects should occur to aquatic organisms at the proposed application rates. Chronic effects to fish and aquatic invertebrates appear unlikely due to low application rates, low toxicity and the method of application.

Endangered species considerations: The maximum terrestrial EEC is just slightly above 1/10 LC_{50} for both mallard duck and bobwhite quail and for small wild mammals. Because the EEC represents the worst case (all seeds exposed) and labeling statements ensure proper planting, the effects to endangered and threatened terrestrial species appears minimal. The maximum aquatic EEC is well below the 1/20 LC_{50} for rainbow trout so application should pose no hazard to endangered freshwater aquatic organisms.

BENEFITS

The oxadixyl end-use product will be used at low use rates for control of seed and seedling diseases caused by Pythium and Phytophthora which affect a large number of economically important crops. Seed treatment may eliminate the need for more costly early season foliar sprays to control diseases caused by these organisms, resulting in lower cost and reduced pesticide usage. This chemical would be an alternative to currently registered pesticides which are prone to development of resistance in fungi. Alternation of chemicals would slow development of resistance since different modes of action are involved. Oxadixyl also has a favorable environmental toxicity profile and low solubility in water which would reduce chances for off-target movement.

TOLERANCE ASSESSMENT

Tolerances are established for the combined residues of the fungicide oxadixyl, [2-methoxy-N-(2-oxo-1,3-oxazolidin-3-yl)-acet-2',6'-xylidide] and its desmethyl or M-3 metabolite, [2-hydroxy-N-(2-oxo-1,3-oxazolidin-3-yl)-acet-2',6'-xylidide], expressed as oxadixyl in or on the following raw agricultural commodities: 0.10 ppm for the fruiting vegetables (except cucurbits) group, cucurbit vegetables group, leafy vegetables (except Brassica vegetables) group, Brassica (cole) leafy vegetables group, cotton seed, peas, soybeans, sunflower seed, root and tuber vegetables group, cereal grains group (except wheat), grass forage, fodder and hay group, and non-grass animal feeds (forage, fodder, straw and hay) group.

The nature of the residue is adequately understood and the Agency concluded that the pesticide is useful for the purposes for which tolerances are sought and that establishment of the tolerances will protect the public health.

The Reference Dose (RfD) based on the 2-year rat feeding study (NOEL of 10.9 mg/kg body weight) and using an uncertainty factor of 100, is calculated to be 0.11 mg/kg body weight/day. The anticipated residue contribution (ARC) of the proposed tolerances is 0.000034 mg/kg body weight/day and utilizes 0.031 percent of the RfD for the total population and the percents of the RfD are 0.074 and 0.058 percent for non-nursing infants and children ages 1 - 6, respectively. Since chronic exposure estimates are less than 1% of the Reference Dose, the risk of toxic effects other than cancer appears to be negligible.

Oxadixyl has been classified as a Group C (possible human) carcinogen with a carcinogenic potency factor (Q_1^*) of 0.053 $(mg/kg/day)^{-1}$. The upper bound carcinogenic risk estimate (1.8×10^{-8}), defined with anticipated residues, may slightly exceed the level generally considered negligible by the Agency. However, the risk estimate is based on the assumption that 100% of the crop that is grown in the U.S. will be treated with this product. This assumption is unrealistic since alternative pesticides are available and disease situations requiring the pesticide will not occur everywhere. A true estimate of the actual use of this chemical is not possible, but realistically, the use level would be less than 100%. Therefore, the carcinogenic risk estimate would reasonably be less than that calculated.

SUMMARY OF MAJOR DATA GAPS

There are no data gaps for the use of oxadixyl as a seed treatment. A field dissipation study must be submitted to support any future registrations for the use of this chemical for foliar applications and field crop rotational data must be submitted if label restrictions regarding rotational crops are to be removed from the label.

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